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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,383	12/06/2005	Klaus Dietzel	27072U	3631

34375 7590 10/13/2010

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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
10/13/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,383	DIETZEL ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *RCE Filed 05 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4 and 6-11 are pending. Applicants amended claims 1-2, 4, and 6. Applicants cancelled claim 5. Receipt and consideration of Applicants' claim amendments and remarks/arguments submitted on October 5, 2010 are acknowledged. All rejections/objections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 5, 2010 has been entered.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-4, 6, 9, and 11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Aberg et al. (U.S. Patent No. 5,795,564) (IDS) in view of Burt (US 2002/0030068), García-Marcos et al. ("Inhaled corticosteroids plus long-acting beta2-agonists as combined therapy in asthma," *Expert Opin. Pharmacother.*, April 2003, *4(1)*, pp 23-39) ("García"), and Calatayud et al. (U.S. Patent No. 5,482,934) (IDS).

Applicant Claims

Applicants claim a pharmaceutical suspension formulation comprising (i) the active particles of ciclesonide, physiologically functional derivative, solvate, or salt thereof, (ii) particles of formoterol, salt, , physiologically functional derivative, fumarate dihydrate thereof,

or solvate thereof, (iii) HFA 134a (i.e. 1,1,1,2-tetrafluoroethane), HFA 227 (i.e. 1,1,1,2,3,3,3-heptafluoropropane), or mixtures thereof, and (iv) optionally surfactant, wherein in some embodiments the surfactant is oleic acid present in an amount ranging from about 0.001-0.1% w/w and other embodiments, wherein the compositions also comprise disodium cromoglycate at a concentration that is not therapeutically or prophylactically effective (i.e. disodium cromoglycate in claim 10 is not considered an active agent) and the only active agents in the compositions in a therapeutically/prophylactically effective amount or R,R,-formoterol and ciclesonide.

NOTE: The recited intended use of the claimed composition of claim 11 is given little patentable weight, because it does not affect the components of the claimed composition.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Aberg exemplifies a metered dose inhaler containing a suspension formulation comprising (i) **R,R-formoterol fumarate dihydrate**, (ii) trichloromonofluoromethane (propellant), (iii) dichlorodifluoromethane (propellant), and (iv) sorbitan trioleate (surfactant) (Example 12: col. 13, lines 3-20). Aberg teaches that commercially available formoterol is a racemic mixture of the "R,R" and the "S,S" enantiomers and is used **as a bronchodilator in the treatment of respiratory diseases, such as asthma** (col. 1, lines 53-55; col. 2, line 63 through col. 3, line 52; col. 5, lines 11-15, and col. 6, lines 45-50). Aberg teaches that utilizing (R,R)-formoterol is desirable due to its diminished adverse effects, decreased development of tolerance, and increased bronchial distribution upon inhalation administration when compared to racemic formoterol (col. 8, lines 5-10). **Aberg teaches that (R,R)-formoterol may be used in**

combination with other therapeutic ingredients and may be formulated into various forms such as **suspensions**, which may be **administered by inhalation** (col. 10, lines 36-60; Example 12: col. 13, lines 3-20; claims 1-3 and 8-12).

Burt teaches that chlorofluorocarbon propellants are being phased out in pharmaceutical formulations, because these propellants deplete the ozone layer [0002] and that **suitable alternative propellants include HFA-134a (1,1,1,2-tetrafluoroethane) and HFA-227 (1,1,1,2,3,3,3-heptafluoropropane)**. Burt identifies several active agents that may be formulated into pharmaceutical compositions in the form of a solution **or a suspension** in combination with HFA propellants, such as **anti-inflammatories (e.g. budesonide, fluticasone, flunisolide, etc.) and bronchodilators (e.g. formoterol)** [0016]. Burt explicitly suggests the combination of a long-acting beta-2 agonist (i.e. salmeterol xinafoate) and an anti-inflammatory steroid (i.e. fluticasone propionate) [0017] in the same pharmaceutical aerosol formulation.

García teaches that data for the **combination of a long-acting beta-2 agonist (e.g. formoterol or salmeterol) with an inhaled corticosteroid (ICS) in the same inhaler is as effective as administration of a much higher dosage of the ICS alone for the control of asthma in patients with asthma that is not well controlled with ICS alone** (abstract; pgs. 23-24, introduction; pg. 34, section 12; and pg. 34-35 1st paragraph of section 13 and last paragraph of section 13) and permits a decreased likelihood of a patient experience side effects from the ICS. Several studies concerning the effectiveness of the combination of formoterol and budesonide in the treatment of asthma are reviewed in section 2.2. García teaches that the **formoterol/budesonide combination was found to improve lung function and asthma control when combined with both low and high doses of budesonide in comparison to**

asthmatics administered only budesonide (pg. 27, left column, paragraph bridging pages 26-27).

Calatayud teaches the syntheses, purification, and isolation of **ciclesonide** and that **ciclesonide is desirable for the treatment of inflammatory conditions**, because it **has a greater therapeutic index** (i.e. a much lower systemic effects and its effects are more localized) **than other commonly administered anti-inflammatory steroids (e.g. budesonide, beclomethasone dipropionate, betamethasone valerate, flunisolide, etc.)** (Abstract; col. 1, lines 64-67; Example VII: col. 10, lines 1-44; Table II, compound 7: columns 17-18; Table III, compound 7 under columns 17-18).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Aberg lacks the teaching of compositions comprising formoterol in combination with ciclesonide. This deficiency is cured by the teachings of (Garcia, Burt, and Calatayud). Aberg lacks the teaching of suspension aerosol formulations comprising HFA-134a and/or HFA 227. This deficiency is cured by the teachings of Burt.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Applicants' invention to combine the teachings of Aberg and Garcia, Burt, and Calatayud, because Aberg teaches that (R,R)-formoterol, a long-acting beta2-agonist (LABA), may be combined with other therapeutic agents, and the combination of LABAs with inhaled corticosteroids has been demonstrated to be

clinically effective and desirable. An ordinary skilled artisan would have been motivated to combine the teachings of the cited references, because these references all described formulations for the treatment of inflammatory diseases (e.g. asthma). An ordinary skilled artisan would have been motivated to combine (R,R)-formoterol with ciclesonide in lieu of other known inhalable corticosteroids, because ciclesonide has a much greater therapeutic index (i.e. lower systemic effects vis-à-vis its localized therapeutic effects). An ordinary skilled artisan would have been motivated to substitute the chlorofluorocarbon propellants present in Aberg's exemplified suspension aerosol formulation for HFA-134a, HFA 227, or combinations thereof, because CFC's are being phased out in pharmaceutical formulations, due to the damage that CFC's do to the ozone layer, and HFA-134a and HFA 227 are art-recognized as suitable pharmaceutically acceptable propellants for use in lieu of CFC's. Thus, an ordinary skilled artisan would have had a reasonable expectation of successfully formulating suspension formulations of formoterol and ciclesonide with HFA-134a, HFA 227, or combinations thereof.

Regarding the presence of ethanol in amounts less than 3%, none of the prior art references suggest or teach formulations comprising ethanol, thus, meeting this claim limitation. Regarding the number of times a day the claimed formulation is administered, this is an intended use of the claimed composition and does not change the composition claimed. Thus, this limitation is given little patentable weight and is met by the prior art teachings suggesting the composition of claim 1. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed October 5, 2010 have been fully considered but they are not persuasive. Applicants have traversed this rejection by attacking the references individually and arguing that (1) allegedly none of the cited references when taken alone or in combination teach or fairly suggest all the elements of the claimed invention and (2) because allegedly the combined prior art does not teach or suggest all the elements of the claimed invention there allegedly is no motivation to obtain the allegedly missing elements from teachings of the cited references.

The Examiner respectfully disagrees with Applicants' traversal arguments. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants' arguments essentially are based on the premise that because Aberg does not anticipate the claims and Burt, Garcia, and Calatayud individually do not cure Aberg's deficiencies that the rejection must be improper. This premise is flawed, because it assumes that the citation of multiple references renders a rejection improper. In response to applicant's implied argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). Applicants' arguments also demonstrate their misunderstanding of the basis of the instant rejection.

The secondary references cited establish that it was well known in the art that (i) chlorofluorocarbons were being phased out in favor of propellants, such as hydrofluorocarbons (HFAs or HFCs), which were not damaging to the ozone layer (Burt); (ii) HFA suspension formulations comprising the combination of a betamimetic bronchodilator (e.g. formoterol) and an anti-inflammatory steroid (e.g. budesonide) were known or fairly suggested (Burt and Garcia); (iii) the combination of an inhaled corticosteroid (e.g. budesonide) and an inhaled beta-2 adrenergic bronchodilator (e.g. formoterol) were known to be as effective as administration of a much higher dose of corticosteroid alone (Garcia); and (iv) ciclesonide is a more desirable anti-inflammatory steroid, than budesonide and other commonly administered anti-inflammatory steroids, because it has a higher therapeutic index. Thus, the ordinary skilled artisan would clearly have been motivated to replace the CFC propellants taught by Aberg with suitable alternative propellants such as HFA's, because CFC's were being phased out. An ordinary skilled artisan knowing that the combination of an inhaled corticosteroid and an inhaled betamimetic bronchodilator (e.g. formoterol) were as effective as a higher dose of inhaled corticosteroid, would have been motivated to modify Aberg to include inhalable corticosteroids. (Garcia), especially given that the prior art had explicitly taught/suggested the combination of bronchodilating betamimetics and anti-inflammatory steroids in HFA suspension formulations. The ordinary skilled artisan would have been motivated to select ciclesonide as the corticosteroid added to Aberg's formulation and not utilize other corticosteroids or to substitute ciclesonide for other corticosteroids, because ciclesonide exhibits a desirable higher therapeutic index than other corticosteroids typically administered by inhalation. It is also noted that Aberg explicitly states that (R,R)-formoterol may be combined with additional therapeutic agents. Thus, for the

aforementioned reasons there is ample motivation to modify the teachings of Aberg to utilize HFA propellants, include anti-inflammatory steroids (i.e. an additional therapeutic agent), and select ciclesonide as the anti-inflammatory steroid. The rejection is maintained.

Claims 2 and 7-8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Aberg et al. (U.S. Patent No. 5,795,564) (IDS) in view of Burt (US 2002/0030068), García-Marcos et al. ("Inhaled corticosteroids plus long-acting beta2-agonists as combined therapy in asthma," *Expert Opin. Pharmacother.*, April 2003, *4(1)*, pp 23-39) ("García"), and Calatayud et al. (U.S. Patent No. 5,482,934) (IDS) as applied to claims 1, 3-4, 6, 9, and 11 above, and further in view of Fassberg et al. (U.S. Patent No. 5,474,759).

Applicant Claims

Applicants claim a composition as described above, comprising a surfactant and in some embodiments the claimed composition may comprise ethanol.

NOTE: The recited intended use of the claimed composition of claim 11 is given little patentable weight, because it does not affect the components of the claimed composition.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Aberg, Garcia, Burt, and Calatayud are set forth above.

Fassberg teaches pharmaceutical aerosol formulations comprising (i) **a medicament in an amount from 0.01-1% w/w, (ii) surfactant in an amount of 0-3% w/w; (iii) excipient (e.g. ethanol) in an amount from 0-75% w/w, and (iv) 1,1,1,2,3,3,3-heptafluoropropane (HFC**

227) (propellant), which was used in lieu of CFC propellants that deplete the ozone layer (title; abstract; col. 1, line 40 through col. 2, line 21). **Preferred surfactants include oleic acid**, sorbitan trioleate, etc. (col. 3, lines 40-55; col. 5, lines 42-46). Surfactants are used to lower the surface and interfacial tension between the medicament and the propellant and may be used in suspension formulations (col. 5, lines 31-35). The excipient facilitates that compatibility of the medicament with the propellant and also lowers the discharge pressure to an acceptable range (col. 4, lines 55-62). **Preferred excipients include ethanol** (col. 5, lines 4-30). Suitable medicaments are those which are delivered by oral or nasal inhalation and include bronchodilators (e.g. albuterol), anti-inflammatory compounds (e.g. mometasone furoate, disodium chromoglycate, beclomethasone dipropionate, etc.) (col. 6, lines 6-21). Fassberg exemplifies various formulations comprising a beta agonist bronchodilator (i.e. albuterol) (see Example 1-18 in columns7 and 8) as well as formulations comprising anti-inflammatory steroids (see Examples 19-33 in columns 8 and 9).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Aberg lacks the teaching of formulations comprising ethanol and/or a surfactant. This deficiency is cured by the teachings of Fassberg.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Applicants' invention to combine the teachings of Aberg and Fassberg, because both references teach inhalable formulations

suitable for the treatment of asthma that can be formulated as aerosol formulations with hydrofluorocarbon propellants. An ordinary skilled artisan would have been motivated to modify the teachings of Aberg to include ethanol and or a surfactant, such as oleic acid, because Fassberg teaches that both ethanol and surfactants can be added to tune the formulation surface tension and facilitate the compatibility of the medicament with the hydrofluorocarbon propellant. An ordinary skilled artisan would have found it prima facie obvious to select ethanol as a possible excipient as well as oleic acid as a possible surfactant, because both ethanol and oleic acid are taught as being a preferred excipient and surfactant, respectively, by Fassberg. Furthermore, it is noted that approximately 1/3 of Fassberg's exemplified compositions contain oleic acid and approximately 1/6 of Fassberg's exemplified compositions contain ethanol. Thus, an ordinary skilled artisan would likely choose both oleic acid and ethanol from the list of preferred excipients and surfactants from which to prepare pharmaceutical aerosol suspension formulations. An ordinary skilled artisan would have had a reasonable expectation of successfully formulating suspension formulations of formoterol and ciclesonide containing ethanol and/or oleic acid, because Fassberg taught that suspension formulations could contain surfactants and/or excipients, such as ethanol.

Regarding the amount of ethanol and oleic acid recited in Applicants' claims, this amount overlaps with the amounts taught as being suitable by Fassberg. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was

made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed October 5, 2010 have been fully considered but they are not persuasive. Applicants have traversed this rejection by reiterating their traversal arguments regarding the first Aberg rejection. The Office's rebuttal of Applicants' traversal arguments is herein incorporated by reference. The rejection is maintained.

Claims 1, 3, 9, and 11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gavin et al. (WO 01/78738) ("Gavin") in view of Calatayud et al. (U.S. Patent No. 5,482,934) (IDS).

Applicant Claims

Applicants' claims have been described above.

NOTE: The recited intended use of the claimed composition of claim 11 is given little patentable weight, because it does not affect the components of the claimed composition.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Gavin teaches medicinal compositions comprising (R,R)-formoterol and rofleponide (i.e. a corticosteroid) for the treatment of respiratory diseases, such as asthma, preferably in the form of inhalable compositions (title; abstract; pg. 1, lines 29-33; pg. 2, lines 12-17, and pg. 3, lines

11-21). (R,R)-formoterol may be used in the form of its fumarate salt (pg. 4, lines 17-20). **The invented compositions may comprise additional therapeutic agents, such as anti-inflammatory agents (e.g. budesonide, beclomethasone dipropionate, triamcinolone acetonide, etc.) or NSAIDS (e.g. sodium cromoglycate)** (pg. 6, lines 1-10). Sodium cromoglycate is synonymous with disodium chromoglycate. Inhalable formulations include powders and **suspension aerosols delivered from pressurized packs with the use of a propellant, such as 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, or mixtures thereof** (pg. 6, line 27 through pg. 7, line 4; Claim 8). The active ingredients in suspension aerosol formulations have a particle size in the range of 1-10 microns, preferably 1-5 microns (Id.). Gavin exemplifies two metered dose inhaler formulations comprising (R,R)-formoterol fumarate, rofleponide, and 1,1,1,2-tetrafluoroethane (pg. 8, lines 5-25).

The teachings of Calatayud are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Gavin lacks the teaching of formulations comprising ciclesonide. This deficiency is cured by the teachings of Calatayud.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Applicants' invention to combine the teachings of Gavin and Calatayud and replace rofleponide in Gavin's formulations with ciclesonide, because Calatayud teaches that ciclesonide has a greater therapeutic index than other

conventional anti-inflammatory corticosteroids. An ordinary skilled artisan would have been motivated to combine the teachings of the cited references, because it is desirable to utilize a corticosteroid with large therapeutic index, such as ciclesonide, to minimize undesirable systemic effects and maximize the desirable local anti-inflammatory effects. An ordinary skilled artisan would have been motivated to utilize HFA-134a, HFA 227, or combinations thereof, because these propellants are taught by Gavin as being suitable for use in pharmaceutical suspension aerosol formulations. Thus, an ordinary skilled artisan would have had a reasonable expectation of successfully formulating suspension formulations of formoterol and ciclesonide with HFA-134a, HFA 227, or combinations thereof. Regarding the presence of ethanol in amounts less than 3%, none of the prior art references suggest or teach formulations comprising ethanol, thus, meeting this claim limitation. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed October 5, 2010 have been fully considered but they are not persuasive. Applicants have traversed this rejection by (1) reiterating their arguments traversing the first Aberg rejection, (2) attacking all the references individually including Gavin, and (3) Gavin is an improper reference because it does not disclose (i.e. anticipate) Applicants' claimed invention.

The Examiner respectfully disagrees with Applicants' traversal arguments. The Office's rebuttal of Applicants' traversal arguments presented regarding the first Aberg rejection as it pertains to the instant rejection are herein incorporated by reference. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants' arguments essentially are based on the premise that because Gavin does not anticipate the claims the rejection must be improper. This line of reasoning is flawed, because the instant rejection is not one based on an anticipation analysis, but rather an obviousness analysis. Regarding (3), the teachings of the combined prior art provide strong motivation to substitute the rofleponide in Gavin's invented compositions for ciclesonide and obtain the claimed composition. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention. Applicants' arguments are unpersuasive and the rejection is maintained.

Claims 2, 4 and 7-8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gavin et al. (WO 01/78738) ("Gavin") in view of Calatayud et al. (U.S. Patent No. 5,482,934) (IDS) as applied to claims 1, 3, 9, and 11 above, and further in view of Fassberg et al. (U.S. Patent No. 5,474,759).

Applicant Claims

Applicants claim a composition as described above, comprising a surfactant and in some embodiments the claimed composition may comprise ethanol.

NOTE: The recited intended use of the claimed composition of claim 11 is given little patentable weight, because it does not affect the components of the claimed composition.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Gavin's teachings are set forth above. The teachings of Calatayud are set forth above.

Fassberg teachings are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Gavin lacks the teaching of formulations comprising ethanol and/or a surfactant. This deficiency is cured by the teachings of Fassberg.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Applicants' invention to combine the teachings of Gavin and Fassberg, because both references teach inhalable formulations comprising anti-inflammatory steroids that can be formulated as aerosols suspensions with hydrofluorocarbon propellants. An ordinary skilled artisan would have been motivated to modify the teachings of Gavin to include ethanol and or a surfactant, such as oleic acid, because Fassberg teaches that both ethanol and surfactants can be added to tune the formulation surface

tension and facilitate the compatibility of the medicament with the hydrofluorocarbon propellant. An ordinary skilled artisan would have found it prima facie obvious to select ethanol as a possible excipient as well as oleic acid as a possible surfactant, because both ethanol and oleic acid are taught as being a preferred excipient and surfactant, respectively, by Fassberg. Furthermore, it is noted that approximately 1/3 of Fassberg's exemplified compositions contain oleic acid and approximately 1/6 of Fassberg's exemplified compositions contain ethanol. Thus, an ordinary skilled artisan would likely choose both oleic acid and ethanol from the list of preferred excipients and surfactants from which to prepare pharmaceutical aerosol suspension formulations. An ordinary skilled artisan would have had a reasonable expectation of successfully formulating suspension formulations of formoterol and ciclesonide containing ethanol and/or oleic acid, because Fassberg taught that suspension formulations could contain surfactants and/or excipients, such as ethanol.

Regarding the amount of ethanol and oleic acid recited in Applicants' claims, this amount overlaps with the amounts taught as being suitable by Fassberg. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed October 5, 2010 have been fully considered but they are not persuasive. Applicants have traversed this rejection by reiterating their traversal arguments regarding the first Gavin rejection. The Office's rebuttal of Applicants' traversal arguments is herein incorporated by reference. The rejection is maintained.

Claims 2, 4, 7-8, and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gavin et al. (WO 01/78738) ("Gavin") in view of Calatayud et al. (U.S. Patent No. 5,482,934) (IDS) as applied to claims 1, 3, 9, and 11 above, and further in view of Keller et al. (WO 00/07567) (IDS)[1], wherein U.S. Patent No. 6,475,467 (Keller) (IDS) is being used as the English language equivalent of WO 00/07567**.**

Applicant Claims

Applicants claim a composition as described above, further comprising disodium chromoglycate in a non-therapeutically and/or non-prophylactically active concentration, and, in some embodiments, ethanol and/or a surfactant (e.g. oleic acid).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Gavin's teachings are set forth above. The teachings of Calatayud are set forth above.

Keller teaches that the inclusion of solid salts of cromoglycic acid and/or nedocromil as a vehicle at non-therapeutically or non-prophylactically effective **concentrations improves the**

dispersion characteristics and the chemical and physical stability or active ingredients which are sensitive to moisture and are present in pharmaceutical aerosol suspension formulations (abstract). **Particularly preferred carrier materials are disodium cromoglycate and nedocromil sodium** (col. 6, lines 32-36). Suitable active agents used in combination with disodium cromoglycate or nedocromil sodium are any that which can be administered as suspended aerosols in therapeutically effective amounts, such as formoterol, formoterol fumarate, and ciclesonide (col. 5, lines 13-29). The aerosol formulations may also **contain a combination of active agents, such as formoterol or a pharmaceutically acceptable derivative, and ciclesonide** (col. 5, lines 36-47).

Keller's compositions do not require the addition of cosolvents or surfactants; however, if a cosolvent and/or surfactant are desired these may be included (col. 4, line 66 through col. 5, line 7 and col. 8, line 59 through col. 9, line 28). Preferred cosolvents, if present, include ethanol (col. 9, lines 4-5). **The amount of cosolvent present is not over about 15% w/w, preferably not over about 10%, usually not over about 5% w/w** (col. 9, lines 8-13). **Suitable surfactants, if present, include oleic acid, and are generally present in an amount ranging from 0.001 to 0.1% w/w** (col. 9, lines 14-28). Keller exemplifies the preparation of an aerosol suspension formulation comprising (i) ~99.93% w/w HFA 227, (ii) ~0.007% w/w of formoterol fumarate, (iii) ~0.014% of disodium cromoglycate, and (iv) ~0.043% of fluticasone propionate in Example 6 (col. 10, lines 50-63).

Keller specifically states that the **inclusion of disodium cromoglycate or nedocromil sodium to formulations can be used to stabilize moisture-sensitive compounds, such as**

[1] Applicants' March 7, 2006 IDS indicated that U.S. Patent No. 6,475,467 is the English language equivalent of WO

formoterol fumarate (col. 4, lines 51-59) as well as **to reduce the tendency to adhesion of electrostatically charged active compounds, such as micronized corticosteroids** (col. 4, lines 60-65).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Gavin lacks the teaching of formulations comprising (i) disodium cromoglycate in a sub-therapeutic amount and (ii) ethanol and/or a surfactant. This deficiency is cured by the teachings of Keller.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Applicants' invention to combine the teachings of Gavin and Keller, because both references teach inhalable formulations comprising anti-inflammatory steroids and/or formoterol fumarate that can be formulated as aerosols suspensions with hydrofluorocarbon propellants (e.g. HFA 227). An ordinary skilled artisan would have been motivated to modify the teachings of Gavin to include disodium cromoglycate to obtain suspension formulations exhibiting improved physical and chemical stability (Keller). Furthermore, an ordinary skilled artisan would have been motivated to include ethanol and or a surfactant, such as oleic acid, because Keller teaches that both ethanol and surfactants can be added to the suspension formulation and specifies suitable amounts of cosolvent and surfactants that can be added if desired. An ordinary skilled artisan would have

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00/07567 (i.e. "corresponds to...").

had a reasonable expectation of combining the teachings of Gavin and Keller, because both references teach HFA-based pharmaceutical suspensions and Keller teaches amounts of disodium cromoglycate as well as amounts of ethanol and oleic acid, if present, that can be suitably co-formulated with compositions comprising medicaments, such as formoterol fumarate and a corticosteroid.

Regarding the amount of ethanol recited in Applicants' claims, this amount overlaps with the amounts taught as being suitable by Keller. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed October 5, 2010 have been fully considered but they are not persuasive. Applicants have traversed this rejection by reiterating their traversal arguments regarding the first Gavin rejection. The Office's rebuttal of Applicants' traversal arguments is herein incorporated by reference. The rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 remains provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 6 of copending Application No. 10/537,356 (copending '356) in view of Burt (US 2002/0030068) and Aberg et al. (U.S. Patent No. 5,795,564) (IDS).

Claim 1 of the instant application has been described above. Independent claim 6 of copending '356 claims a formulation comprising R,R-formoterol and ciclesonide in a form administrable from a dry powder inhaler. The difference between claim 1 of the instant application and claim 6 of copending '356 is that the composition of the instant application is a suspension formulation (i.e. it comprises insoluble particulate formoterol and particulate ciclesonide) and claim 1 of the instant application does not specify that formoterol is (R,R)-formoterol. Regarding (R,R)-formoterol, the use of this enantiomer is prima facie obvious at the time of the instantly claimed invention, because it was known to be the broncho-active enantiomer of the commercially available racemic formoterol mixture (Aberg). Regarding conversion of a mixture of particulate formoterol and ciclesonide into a suspension, this requires the mere addition of HFA propellant, which can be done by various well known procedures (e.g.

cold filling of the propellant into a metered dose inhaler pre-filled with a particulate mixture). Furthermore, inhalable aerosol suspensions are one of the conventionally used inhalable formulations (i.e. (i) inhalable aerosol solutions, (ii) inhalable aerosol suspensions, (iii) propellant-free solutions, (iv) propellant-free suspensions, and (v) inhalable powders). Aerosol suspensions comprising a mixture of a beta2-agonist with an anti-inflammatory steroid are well known (Burt). Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 1 and 5 *prima facie* obvious over claim 6 of copending Application No. 10/537,356 (copending '356) in view of Burt (US 2002/0030068) and Aberg et al. (U.S. Patent No. 5,795,564) (IDS).

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicant's arguments filed October 5, 2010 have been fully considered but they are not persuasive. Applicants did not traverse the instant rejection, but requested that the rejection be held in abeyance until the indication of allowable subject matter. Because there is no provision in the MPEP for a rejection to be held in abeyance and Applicants do not traverse the propriety of the rejection, the instant rejection is maintained.

Conclusion

Claims 1-4 and 6-11 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, ~10:00-6:00 and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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